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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/991,628	11/05/1997	JACK L. STOMINGER	HUIP-P02-001	2823

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/991,628	STOMINGER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/24/04 and 6/17/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6, 11, 30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6, 11, 30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/24/04 has been entered.

2. Applicant's amendments filed 11/24/04 and 6/17/04 are acknowledged and have been entered.

Claims 3-6, 11, 30 and 31 are pending and are presently being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3-6, 11, 30 and 31 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed inventions.

The instant claims encompass: (1) a pharmaceutical preparation for tolerization comprising a pharmaceutically acceptable carrier and (a) an "isolated human polypeptide" or (b) an "isolated human pathogen polypeptide" effective for tolerizing an individual to an autoantigen, said human polypeptide consisting of a sequence motif for an HLA-DR protein containing the core MHC binding residues, wherein said HLA-DR protein is selected from the group consisting of HLA-DR2 and HLA-DR4 associated with one of the human autoimmune diseases PV or MS, wherein the polypeptide binds the said HLA-DR protein and activates autoreactive T cells from a subject having the said autoimmune disease and wherein the polypeptide is a non-MBP polypeptide, or (4) a method of tolerizing an individual to an autoantigen of PV comprising administering an effective amount of the pharmaceutical preparation of "(1)(a)" above to a subject in need of such treatment. The instant claims encompass a

pharmaceutical composition comprising a polypeptide that binds to an HLA-DR2 or HLA-DR4 allele and activates autoreactive T cells from a subject having PV or MS, wherein the said HLA-DR2 or HLA-DR4 allele is associated with PV or MS and wherein the polypeptide does not have to be a subsequence of an autoantigen associated with PV or MS, nor a subsequence of some undisclosed polypeptide of undisclosed structure that is exclusively found in humans or in human pathogens or a method of tolerizing a patient to an autoantigen of PV comprising administering a pharmaceutical composition that comprises a polypeptide that is not necessarily a subsequence from the PV-associated autoantigen desmoglein-3.

The specification does not it provide adequate written description for a pharmaceutical preparation for tolerization comprising an "isolated human polypeptide" or "an "isolated human pathogen polypeptide"...consisting of a sequence motif for an HLA-DR4 or HLA-DR2 protein containing the core MHC binding residues" that "activates autoreactive T cells from a subject having PV or MS" nor does it provide adequate written description of what those MHC core binding residues are, nor of the structure of HLA-DR2 or HLA-DR4 protein peptide binding site and associated sequence motifs, nor of a method for tolerizing an individual to an autoantigen of PV comprising administering the preparation of "(1)(a)" above. The specification does not disclose what amino acid residues are associated with a *human* polypeptide or a *human* pathogen polypeptide.

The specification on page 52 at lines 25-27 discloses that the term "core MHC binding residues" means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31). Accordingly, the amino acids at a maximum of three of the P1, P4, P6, P7 and P9 motif positions in the peptide may not be motif amino acids and may actually be deleterious to binding. The PV motif #1 of instant claim 5 has only three defined positions, P1, P4 and P6.

The specification discloses (page 15 at lines 20-23) the pocket 1 amino acid residues for HLA-DRβ1*0101, and that the "corresponding residues for other HLA-DR alleles are known in the art (see, e.g., Marsh and Bodmer, 1992, incorporated by reference herein) and are available through genetic databases." The specification does not disclose which HLA-DR alleles are known in the art at the time the invention was made, nor what the structure of the peptide binding site is for each corresponding HLA-DR allele, nor what the sequence motif is, nor what the core binding residues are. The specification further discloses that "...before or after the pockets to be restricted by the motif are selected, the set of amino acid side chains likely to bind within each of those

pockets, and therefore, the set of amino acid residues that will define the corresponding positions of the motif, must be determined. This may be accomplished by one of ordinary skill in the art by considering the amino acid residues which form the pocket. These residues, identified in Section A above, will determine the size and nature (i.e., hydrophobic, hydrophilic, positively charged, negatively charged, uncharged) of the pocket and consequently, the side chains which may bind within the pocket." (page 20 at the second paragraph). The specification discloses for one of the identified pockets P6, that the alpha chain amino acid pocket residues are relatively conserved among HLA-DR molecules, but that the two beta chain amino acid residues, β11 and β13 vary widely among the DR alleles (page 17 at the two full paragraphs). The specification further discloses that in DR alleles wherein b13 is occupied by smaller or more polar residues such as the β 13 His of DR β1*0401, the P6 motif may include somewhat larger and polar residues (e.g., S, T, V) but should still avoid the largest and aromatic residues, and in some alleles β11 and β13 are both serine residues (e.g., DRβ1*1101) and for these cases more hydrophilic or hydrogen bonding residues may be included in the motif (page 17 at the second full paragraph).

Evidentiary reference Rammensee et al (MHC Ligands and Peptide Motifs, 1997, pages 204-205) teaches that for alleles that possess β11 and β 13 that are both serine residues, the anchor residues are actually large basic amino acid residues (R, K, H) for DRβ1*1101 and DRβ1*1104, and (R, K) for DR β1*1301 and DR β1*1302, in contrast to Applicant's disclosure of the general class of hydrophilic or hydrogen bonding residues which would include acidic amino acid residues. Rammensee et al further teaches that the anchor residues for DR β1*0401 are N, S, T, Q, H, R, the said residues including the "largest and aromatic residues" that Applicant's disclosure predicts should be avoided based upon the structure of the P6 pocket.

The specification discloses that HLA-DR4 (DRβ1*0402) or a rare HLA-DQ1 (DQβ1*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris (PV), and that HLA-DRβ1*1501, i.e., HLA-DR2, or DQ1 are associated with MS disease susceptibility (page 2). Other than HLA-DRβ1*0402, no other HLA-DR4 subtypes are disclosed by the specification as being associated with susceptibility to PV, and other than HLA-DRβ1*1501, no other HLA-DR2 subtypes are disclosed by the specification as being associated with susceptibility to MS.

The specification discloses (page 37 at line 8 through page 38) that although the autoantigen for PV is known (i.e., desmoglein 3, 130kDA, 999 amino acid residues in length), the precise epitopes within the autoantigen have remained previously unknown, and that using the method of the present invention (i.e., the PV#1 motif), a set of 7 peptides were identified that matched the motif and that may be potential autoantigenic determinants for T cell dependent induction of PV. The specification further discloses that T cell lines were raised from blood mononuclear cells of two patients with active

disease, expanded in rIL-2 and tested for recognition of the candidate peptides, the result being that SEQ ID NO: 3 and 4 (two peptides from the extracellular domain of desmoglein 3 that are located close to the major autoantibody recognition site) were recognized. The specification does not disclose if the other 5 peptides are capable of binding to HLA-DR4 (DRβ1*0402, DR4Dw10), nor if they can be recognized by atuoreactive T cells from PV patients, nor if they can be used for immunization or tolerization in such patients or in vitro.

Evidentiary reference O'Sullivan (Applicant's IDS reference) teaches that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and non-binders may have the putative motif.

The specification discloses that the peptide may be administered in high doses to produce high dose tolerance (page 30 at lines 15-18), i.e., that peptides that are immunogenic can be used at high doses to induce tolerance.

The art recognizes that in order to be used for generating an immunogenic or tolerogenic response that said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding.

Evidentiary reference Karin et al (J. Exp. Med. 1994, 180: 2227-2237) teaches that a single substitution in an amino acid residue, wherein said amino acid residue plays no role in MHC binding, can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially summary and Table 1). Thus Karen et al establish that amino acid residues not recited in the claimed "human" or "human pathogen" polypeptides will play a pivotal role in determining whether the peptides recited in the claims are capable of being immunogenic, and by extension tolerogenic.

There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim. With the exception of the specific peptides identified by amino acid sequence in the specification such as SEQ ID NO: 1-7 from the contiguous sequence of the PV autoantigen protein desmoglein 3, the skilled artisan cannot envision the detailed structure of the encompassed peptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

The specification does not disclose which amino acid residues or sequences of amino acid residues are associated with a "human polypeptide", nor with "human pathogen polypeptide". The specification discloses (on page 51 at the last 7 lines) that by "human pathogen" it is meant a bacterium, a virus or a protozoan capable of infecting humans and generating an immune response. The specification does not disclose which amino acid residues are associated with "human pathogen polypeptides" that infect other species as well as humans. There is no disclosure of any "human pathogen polypeptide" that is associated with PV, nor of any "isolated human polypeptide" or protein comprising a subsequence that is an" isolated human polypeptide" other than those that derive from desmoglein-3 for PV.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

Applicant's arguments in the amendment filed 6/17/04 have been fully considered but are not persuasive.

Applicant's position in the said amendment beginning on page 6 and continuing on to page 10 is of record.

It is the Examiner's position that a definition by function in the absence of sufficient structural information does not provide adequate written description for the reasons enunciated in this rejection. A definition by function does not suffice to define the genus because it is only an indication of what the property the peptide has, and if one extends the analysis in the instant case, what the peptide does (i.e., it binds to an HLA-DR2 or an HLA-DR4 molecule and activates autoreactive T cells from a subject having PV or MS), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

It is the Examiner's further position that SEQ ID NO: 1 of the cited Example 9 of the Written Description Guideline's Training Materials is a fully defined sequence (with functional property of binding a specific receptor to stimulate a specific activity) that would yield structurally similar DNAs under stringent hybridization conditions, whereas the instant case is of a polypeptide that may or may not be a subsequence of some undisclosed protein that may or may not be an autoantigen of PV or MS or a protein from an undisclosed pathogen that may be derived from a partial binding motif that is in turn derived in many cases from predictions made from HLA-DR2 or HLA-DR4 allele pocket amino acid residues, and may not in fact stimulate a T cell, and in addition, where the polypeptide is not a subsequence of a protein, the TCR contact amino acid residues may be any of a large number of possible amino acid residues. In the said Example 9, fully defined sequences would be derived from the said hybridization, in contrast to the instant case, and so one of ordinary skill in the art would expect substantial variation among species. It is the Examiner's position that the claims are not limited to a polypeptide that is a subsequence of desmoglein-3. With regard to Applicant's argument as to MBP 15-mer peptide 85-99 being the known epitope in MS, so that specific TCR binding a defined epitope must have relatively conserved sequences depending upon the specific presenting subtypes and/or known subgroups of TCRs specific for the epitope, evidentiary reference Tisch and McDevitt teaches that "the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS... in which there are responses to several autoantigens and the critical inciting autoantign(s) is not known", and the instant claims are not drawn to MBP peptides, and further that the MS

motifs that define permissible TCR contact residues are not recited in the instant claims and are based upon reactivity of a small subgroups of T cell clones to one MBP peptide.

5. Claims 3-6, 11, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3-6, 11, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical preparation comprising a human polypeptide consisting of one of SEQ ID NOS: 3 and 4, does not reasonably provide enablement for the claimed pharmaceutical preparation comprising one of SEQ ID NO: 1, 2, 5, 6 or 7, nor an "isolated human polypeptide" or an "isolated human pathogen polypeptide" consisting of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR2 or an HLA-DR4 protein associated with PV and wherein the said polypeptide activates autoreactive T cells from a subject having PV or MS, nor a method of tolerizing an individual to an autoantigen of PV comprising administering the said pharmaceutical composition comprising the polypeptide wherein the polypeptide is not one of SEQ ID NO: 3 or SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not disclose how to make/and or use the claimed invention. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass: (1) a pharmaceutical preparation for tolerization comprising a pharmaceutically acceptable carrier and (a) an "isolated human polypeptide" or (b) an "isolated human pathogen polypeptide" effective for tolerizing an individual to an autoantigen, said human polypeptide consisting of a sequence motif for an HLA-DR protein containing the core MHC binding residues, wherein said HLA-DR protein is selected from the group consisting of HLA-DR2 and HLA-DR4 associated with one of the human autoimmune diseases PV or MS, wherein the polypeptide binds the said HLA-DR protein and activates autoreactive T cells from a subject having the said autoimmune disease and wherein the polypeptide is a non-MBP polypeptide, or (2) a method of tolerizing an individual to an autoantigen of PV comprising administering an effective amount of the pharmaceutical preparation of "(1)(a)" above or comprising administering a pharmaceutical preparation comprising one of SEQ ID NO: 1, 2, 5, 6, or 7, said SEQ ID NO may or may not bind an HLA-DR4 or an HLA-DR2 allele and be capable of stimulating an immune response or inducing tolerance, to a subject in need of such treatment. The instant claims encompass a pharmaceutical composition comprising a polypeptide that binds to an HLA-DR2 or HLA-DR4 allele and activates autoreactive T cells from a subject having PV or MS, wherein the said HLA-DR2 or HLA-DR4 allele is associated with

PV or MS and wherein the polypeptide does not have to be a subsequence of an autoantigen associated with PV or MS, nor a subsequence of some undisclosed polypeptide of undisclosed structure that is exclusively found in humans or in human pathogens or a method of tolerizing a patient to an autoantigen of PV comprising administering a pharmaceutical composition that comprises a polypeptide that is not necessarily a subsequence from the PV-associated autoantigen desmoglein-3.

The specification on page 52 at lines 25-27 discloses that the term "core MHC binding residues" means the residues of an epitope corresponding to the P-1 to P-9 positions of a peptide bound to an HLA-DR molecule. The specification further discloses that there are 5 binding pockets in MHC (class II, DR), P1, P4, P6, P7 and P9 (page 19 at lines 17-25), at least two of which (page 19 at lines 29-31, page 20, lines 5-6) are used via consideration of the chemical nature and size of said binding pockets (page 20 at lines 9-23) for determination of the sequence motif of the corresponding peptide that binds to the MHC molecule (page 19 at lines 29-31). Accordingly, the amino acids at a maximum of three of the P1, P4, P6, P7 and P9 motif positions in the peptide may not be motif amino acids and may actually be deleterious to binding. The PV motif #1 of instant claim 5 has only three defined positions, P1, P4 and P6.

The specification discloses (page 15 at lines 20-23) the pocket 1 amino acid residues for HLA-DRβ1*0101, and that the "corresponding residues for other HLA-DR alleles are known in the art (see, e.g., Marsh and Bodmer, 1992, incorporated by reference herein) and are available through genetic databases." The specification does not disclose which HLA-DR alleles are known in the art at the time the invention was made, nor what the structure of the peptide binding site is for each corresponding HLA-DR allele, nor what the sequence motif is, nor what the core binding residues are. The specification further discloses that "...before or after the pockets to be restricted by the motif are selected, the set of amino acid side chains likely to bind within each of those pockets, and therefore, the set of amino acid residues that will define the corresponding positions of the motif, must be determined. This may be accomplished by one of ordinary skill in the art by considering the amino acid residues which form the pocket. These residues, identified in Section A above, will determine the size and nature (i.e., hydrophobic, hydrophilic, positively charged, negatively charged, uncharged) of the pocket and consequently, the side chains which may bind within the pocket." (page 20 at the second paragraph). The specification discloses for one of the identified pockets P6, that the alpha chain amino acid pocket residues are relatively conserved among HLA-DR molecules, but that the two beta chain amino acid residues, β11 and β13 vary widely among the DR alleles (page 17 at the two full paragraphs). The specification further discloses that in DR alleles wherein b13 is occupied by smaller or more polar residues such as the β 13 His of DR β1*0401, the P6 motif may include somewhat larger and polar residues (e.g., S, T, V) but should still avoid the largest and aromatic residues, and in some alleles β11 and β13 are both serine residues (e.g., DRβ1*1101)

and for these cases more hydrophilic or hydrogen bonding residues may be included in the motif (page 17 at the second full paragraph).

Evidentiary reference Rammensee et al (MHC Ligands and Peptide Motifs, 1997, pages204-205) teaches that for alleles that possess β11 and β 13 that are both serine residues, the anchor residues are actually large basic amino acid residues (R, K, H) for DRβ1*1101 and DRβ1*1104, and (R, K) for DR β1*1301 and DR β1*1302, in contrast to Applicant's disclosure of the general class of hydrophilic or hydrogen bonding residues which would include acidic amino acid residues. Rammensee et al further teaches that the anchor residues for DR β1*0401 are N, S, T, Q, H, R, the said residues including the "largest and aromatic residues" that Applicant's disclosure predicts should be avoided based upon the structure of the P6 pocket.

The specification discloses that HLA-DR4 (DRβ1*0402) or a rare HLA-DQ1 (DQβ1*05032) allele (page 2) are associated with the autoimmune disease pemphigus vulgaris (PV), and that HLA-DRβ1*1501, i.e., HLA-DR2, or DQ1 are associated with MS disease susceptibility (page 2). Other than HLA-DRβ1*0402, no other HLA-DR4 subtypes are disclosed by the specification as being associated with susceptibility to PV, and other than HLA-DRβ1*1501, no other HLA-DR2 subtypes are disclosed by the specification as being associated with susceptibility to MS.

The specification discloses (page 37 at line 8 through page 38) that although the autoantigen for PV is known (i.e., desmoglein 3, 130kDA, 999 amino acid residues in length), the precise epitopes within the autoantigen have remained previously unknown, and that using the method of the present invention (i.e., the PV#1 motif), a set of 7 peptides were identified that matched the motif and that may be potential autoantigenic determinants for T cell dependent induction of PV. The specification further discloses that T cell lines were raised from blood mononuclear cells of two patients with active disease, expanded in rIL-2 and tested for recognition of the candidate peptides, the result being that SEQ ID NO: 3 and 4 (two peptides from the extracellular domain of desmoglein 3 that are located close to the major autoantibody recognition site) were recognized. The specification does not disclose if the other 5 peptides are capable of binding to HLA-DR4 (DRβ1*0402, DR4Dw10), nor if they can be recognized by atuoreactive T cells from PV patients, nor if they can be used for immunization or tolerization in such patients or in vitro.

Evidentiary reference O'Sullivan (Applicant's IDS reference) teaches that the presence of putative binding motif residues does not necessarily correlate with actual binding to an MHC molecule because both binders and non-binders may have the putative motif. The art recognizes that in order to be used for generating an immunogenic or tolerogenic response that said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding.

There is no written disclosure in the specification of the amino acids that constitute the potential/actual T cell epitope residues in the polypeptide recited in the claims, with the exception of the fully defined sequences disclosed in the specification.

Evidentiary reference Karin et al (J. Exp. Med. 1994, 180: 2227-2237) teaches that a single substitution in an amino acid residue, wherein said amino acid residue plays no role in MHC binding, can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially summary and Table 1). Thus Karen et al establish that amino acid residues not recited in the claimed "human" or "human pathogen" polypeptides will play a pivotal role in determining whether the peptides recited in the claims are capable of being immunogenic, and by extension tolerogenic. Evidentiary reference Tisch and McDevitt (PNAS USA 91: 437-7, 1994) teaches that "the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS..in which there are responses to several autoantigens and the critical inciting autoantigen(s) is not known...Only in EAE, where defined antigens (MBP or the MBP peptide AC1-11) have been used to induce disease, has antigen-specific immunotherapy clearly succeeded in treating an ongoing immune response." Evidentiary reference Smilek et al (PNAS USA 88: 9633-9637, 1991) teach that a single amino acid change in a myelin basic protein peptide confers the capacity to prevent rather than induce EAE. Evidentiary reference Anderton (Immunology 104: 367-376, 2001) teaches that in vivo use of altered peptide ligands is unpredictable and dangerous in outbred human populations (especially paragraph spanning columns 1 and 2 on page 370). Evidentiary reference Chen et al (J. Immunol. 157: 3783-3790, 1996) teach that analogue peptides with single amino acid residue substitutions that bind to HLA-DR4 were unpredictable in that some exhibit agonist activity, others exhibit antagonist activity, and still others exhibit antagonist activity with partial activation. Chen et al further teach that activation mediated by TCR recognition of the ligand is not an on/off event, and it may be quantitatively or qualitatively different depending on affinity and avidity between TCRs and their ligands.

The specification does not disclose which amino acid residues or sequences of amino acid residues are associated with a "human polypeptide", nor with "human pathogen polypeptide". The specification discloses (on page 51 at the last 7 lines) that by "human pathogen" it is meant a bacterium, a virus or a protozoan capable of infecting humans and generating an immune response. The specification does not disclose which amino acid residues are associated with "human pathogen polypeptides" that infect other species as well as humans. There is no disclosure of any "human pathogen polypeptide" that is associated with PV, nor of any "isolated human polypeptide" or protein comprising a subsequence that is an" isolated human polypeptide" other than those that derive from desmoglein-3 for PV.

The specification discloses that the peptide may be administered in high doses to produce high dose tolerance (page 30 at lines 15-18), i.e., that peptides that are immunogenic can be used at high doses to induce tolerance. In addition, the WO 94/06828 document cited (on page 30 at lines 15-18) in the instant specification that is relied upon for disclosure that the peptide may be administered in high doses to produce high dose tolerance teaches substituted tolerizing peptides, i.e., peptides that are generated by replacing each amino acid of the immunogenic peptide with a different amino acid residue and testing for tolerized T cells, i.e., ones that will not proliferate when stimulated with low antigen concentrations.

Evidentiary reference Sercarz (Nature Biotechnology 21(9): 1017-1019, 2003) teaches that to date, not one autoimmune disease has been successfully treated using a specific vaccine, and that typically, in those autoimmune diseases driven by proinflammatory T cell activity (e.g. MS), a plethora of antigens appear to be involved, making it difficult to attempt to devise a single specific tolerogenic vaccine. Sercarz further teaches that because appropriate experimental tolerance-inducing regimens have often failed to be chosen, the potential of a vaccine containing numerous antigens to exacerbate (rather than ameliorate) an autoimmune condition has been an understandable concern.

Evidentiary reference Schwartz and Kipnis (The Neuroscientist 8(5): 405-413, 2002) teaches that in patients with Ms where the aim is to block the autoimmune disorder while deriving the potential benefit of the autoimmune response, the effect of treatment should be immunomodulatory rather than immunosuppressive.

There is no guidance in the specification as to what alterations result in a functional polypeptide, i.e., one that binds to HLA-DR (except for 3 defined of 5 [of an HLA-DR4] binding positions) and to a TCR and causes tolerization. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions/additions would be acceptable to retain functional activity, i.e., bind to any number of undisclosed HLA-DR molecules, bind to a T cell and cause tolerization, it would require undue experimentation for one of skill in the art to arrive at amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make and/or use the corresponding sequences. The enablement provided by the specification is not commensurate with the scope of the claims.

Applicant's arguments in the amendment filed 6/17/04 have been fully considered but are not persuasive.

Applicant's position in the said amendment beginning on page 10 and continuing on through page 13 is of record.

It is the Examiner's position that a larger polypeptide may bind to the same HLA-DR molecule with a different frame of binding than the desired frame of binding depending upon what the actual sequence is and if it contains a binding motif in another frame, in contrast to Applicant's assertion that the larger polypeptide likely binds to an HLA molecule other than the one recognizing the intended frame of binding. If such polypeptide were to bind in an alternate frame, then the TCR contact residues would be different. With regard to Applicant's arguments as to making functionally equivalent molecules based upon for example fixing the P1, P4 and P6 positions according to the relevant motif, the skilled artisan would have to make 20^7 different peptides (i.e., 1,280,000,000 or about 1 billion peptides) and screen them not only for binding to the relevant HLA-DR molecule(s), but also determine which are immunogenic and/or tolerogenic. In addition, in response to this and to Applicant's argument that Applicant has addressed that the structural element or sequence motif is coupled to the functional assay to define the claimed invention, it is the Examiner's position that the sequence motifs even for PV#1 is not fully defined, and that for other HLA-DR2 or HLA-DR4 alleles, knowledge of the pocket amino acid residues alone is not sufficient for determination of a binding motif as enunciated in the instant rejection.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 3-6, 11, 30 and 31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 30 are indefinite in the recitation of "consisting of a sequence motif for an HLA-DR protein containing the core MHC binding residues" because it is not clear what is meant, i.e., (i) if an HLA-DR-binding polypeptide is meant or not, and (ii) if the polypeptide consists of a sequence motif containing the core MHC binding residues, it only contains the core residues and no others.

b. Claims 1 and 30 are indefinite in the recitation of "selected from Pemphigus Vulgaris (PV) and Multiple Sclerosis (MS)" because the recitation is improper Markush language. It is suggested that Applicant amend said claim to recite "selected from the group consisting of Pemphigus Vulgaris (PV) and Multiple Sclerosis (MS)" or "selected from Pemphigus Vulgaris (PV) ***or*** Multiple Sclerosis (MS)". In addition, the Examiner notes that both disease names are capitalized.

c. Claim 5 is indefinite in the recitation of "PV motif #1" because it is not clear what is meant. It is suggested that Applicant amend said claim to recite the amino acid residues permissible at the positions of the said motif.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 3-6, 11, 30 and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 and 4 of U.S. Patent No. 5,874,531. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition comprising the peptides of claims 3 and 4 of the '531 patent are encompassed by the instant claims.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 3 is rejected under 35 U.S.C. 102(a) as being anticipated by Ohashi et al (Dev. Neuroscience 17(3): 189, July 8-10, 1995, Abstract).

Ohashi et al teach polypeptide PLP 95-116 is an HLA-DR2 associated T cell epitope in MS.

Although the abstract of Ohashi et al does not teach the peptide in a pharmaceutical preparation, in order to have determined that the said polypeptide is a T cell epitope, the peptide would necessarily have been dissolved in a carrier compatible with viability of human T cells, i.e., a pharmaceutically acceptable carrier.

Therefore, the claimed preparation appears to be the same or similar to the preparation of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the preparation of the instant invention to

that of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

12. Claim 3 is rejected under 35 U.S.C. 102(a) as being anticipated by Kondo and Ohashi (Nippon Rinsho. Japanese Journal of Clinical Medicine. 52(11): 2940-2945, 11/1994, Abstract).

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14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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